

WRITTEN REQUEST

The Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act (the Act), to obtain needed pediatric information for Nitroprusside. We request that you submit information from trials in pediatric patients as described below.

Strategy

The requested data will provide guidance for the use of Nitroprusside to reduce blood pressure (BP) in pediatric patients. These data will be derived from:

- a dose-ranging trial examining the effects of Nitroprusside in pediatric patients requiring controlled reduction of blood pressure, including patients requiring relative hypotension during a surgical or medical procedure;
- a trial examining the persistence of Nitroprusside's effect on BP during stable infusion regimens and following short-term withdrawal of Nitroprusside.
- safety data derived from the controlled trials and a 1-year follow-up period for patients enrolled in the trial, as well as a summary of all available information on the safety of Nitroprusside in pediatric patients. The safety summary should include a summary of published literature as well as formal analyses of published and unpublished data on the use of Nitroprusside in children. Unpublished data should be sought from organizations participating in healthcare delivery to the pediatric population.

Pediatric Subgroups

Age groups

The five pediatric age groups to which we refer in this document are:

- neonates (age less than one month),
- infants and toddlers (age 1 month – <2 years),
- pre-school children (age 2 – <6 years),
- school-age children (age 6 – <Tanner stage 3), preferred group for effectiveness study, and
- adolescents (Tanner stage 3 – <17 years).
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With respect to effectiveness, the studies described below will include patients from each of the age groups, with at least 50% pre-pubertal patients of whom at least 50% are neonates or toddlers at the time of enrollment, as the course of disease and the effects of drugs in older children are less likely to differ from the course and effects in adults.

Formulation Issues

Since the formulation to be used is an intravenous formulation, appropriate instructions should be supplied for dilution of the formulation for the large weight range for the pediatric population. Furthermore, it is likely that an acceptable dose ranging study will require flexibility in the rate of infusions (the range of doses will likely range over 30 fold). The volume that can be safely infused into pediatric patients is limited.

Consequently, the trials should allow for the large dose range while still allowing flexibility in potential infusion doses.

Any delivery device to be used for administering the intravenous formulation should be routinely available. The delivery device system should be chosen to minimize dead space.

Dose-Ranging Trial

The first trial is intended to describe the acute effects of Nitroprusside on blood pressure (BP) over a range of doses. The goal is to describe the relationship between the infusion rate and changes in BP. The primary efficacy parameter to be measured should be change in blood pressure (systolic, diastolic or mean), compared with baseline. The effect of nitroprusside on heart rate is an important secondary efficacy parameter.

Objectives

- 1) To define the onset and offset of blood pressure lowering effects of nitroprusside to obtain adequate instructions for dose titration.
- 2) To construct a pharmacokinetic/pharmacodynamic model that defines the relationship between nitroprusside infusion rate and changes in blood pressure.

Design

This trial will be a randomized, double-blind, parallel-group, dose-ranging study. The population will be limited to those patients whose blood pressure needs to be controlled acutely and patients whose BP is likely to need control for at least 2 hours (see below). Patients are to be randomized to one of four initial rates of Nitroprusside infusion ranging between 10 and 100 percent of the starting adult dose of 3 micrograms/kg/min. The start of the infusion should only begin once anesthesia has been stabilized and stable vital sign measurements have been obtained. Infusion rates should be up- or down- titrated at intervals of no less than every 10 minutes or until three measurements two minutes apart have established that vital signs have stabilized. The dose will be further up-titrated to a maximum dose that affords the optimum blood pressure control to be defined by the investigator. Excessive drops in blood pressure or increases in heart rate (to be defined by in the protocol) would be sufficient reason to decrease infusion rates earlier than 10 minutes.

Vital signs (systolic and diastolic blood pressure and heart rates) will be monitored frequently (as defined by the investigators but generally at least every 5 minutes) during the start of anesthesia to define baseline measurements (pre-nitroprusside infusion). Frequent measurement of vital signs is also necessary for the first 30 minutes following initiation of nitroprusside, and for 15 minutes following any dose-escalation of nitroprusside. Once a stable dose of Nitroprusside has been identified (3 successive systolic blood pressure readings within 5 mm Hg) vital signs can be obtained less frequently at the discretion of the investigators (*e.g.*, every 15 minutes).

Safety

The following items are required in addition to the standard collection of safety events.

- Significant hypotension or tachycardia should be defined by the investigators and its occurrence monitored during the trial.
- Adverse events occurring from the initial time of Nitroprusside administration until hospital discharge will be systematically collected and reported. Any adverse events that occur during surgery, during the recovery room period as well as during the duration of hospital stay is to be captured and submitted as part of the study report, as should any need for drug intervention (including altering the degree of anesthesia). The circumstances of any deaths, discontinuations and serious adverse events will be adequately documented and transmitted within the study report. Patients with ongoing adverse events at the time of hospital discharge need to be followed until the resolution of adverse event.
- Methemoglobin as well as thiocyanate and cyanide levels should be monitored during the nitroprusside infusion.

Inclusion/Exclusion Criteria

Patients will be enrolled who are to undergo surgical procedures that require blood pressure be controlled for at least 2 hours (*e.g.*, Harrington rod placement, hip dysplasia repair, some surgical procedures which require cardiopulmonary bypass) or surgical settings where controlled hypotension is considered necessary [some Extracorporeal Membrane Oxygenation (ECMO) patients]. Patients who are to have shorter durations of surgery requiring a shorter duration of controlled anesthesia may be enrolled, but they should be no more than 25% of enrollment. The prior use of other drugs to lower BP would neither exclude patients from consideration nor a requirement of entry.

Number of Patients to be Studied

This trial will be sized appropriately to demonstrate a relationship between infusion rate of Nitroprusside or its concentration and blood pressure reduction. Previous trials studying the use of intravenous drugs in the treatment of acute hypertension have required approximately 20 adult patients per treatment arm to demonstrate a dose-response curve with regard to blood pressure lowering. Given the anticipated heterogeneity of the proposed population, the large potential uncertainty around measurement of BP and the use of infusion rates rather than serum concentrations of Nitroprusside, the trial will require a larger sample size of at least 50 patients per treatment group.

Duration

Patients should be treated for the duration of the anesthesia. Patients should be down-titrated, if possible, prior to discontinuation of the anesthesia, with vital signs measured and Nitroprusside infusion rates tabulated during constant levels of anesthesia to determine the offset effects of the various infusion rates, to describe any hysteresis pattern that occurs and to assess for the occurrence of rebound hypertension. Vital signs and adverse events should be collected for the duration of the hospitalization.

Data Analysis

It is unclear if a micro-assay requiring < 0.2 cc of blood exists which can accurately measure Nitroprusside levels *ex vivo*. If such an assay is available, it should be used in the performance of pharmacokinetic/pharmacodynamic analysis and in assessing the relationship between Nitroprusside concentrations *in vivo* and any observed toxicities. As the primary intent of the present study is to describe the use of Nitroprusside in pediatric population, understanding the relationship between infusion rate and BP is of primary importance.

The goal of this study is the derivation of a pharmacokinetic/pharmacodynamic model that describes the relationship of infusion rate to BP. The analysis model to be used will be pre-specified (*e.g.*, mixed effect modeling). This model will analyze the potential interactions of relevant demographics (*e.g.*, baseline blood pressure, age, gender, race, body size) with the time-course of the onset of blood pressure lowering effects of nitroprusside and the time-course of blood pressure increases following Nitroprusside discontinuation.

Trial Assessing Effects of Long-term Infusion

Objectives

- 1) To determine the persistence of Nitroprusside's effect on vital signs during stable infusion regimens lasting ≥ 12 hours.
- 2) To assess the potential for rebound following administration of Nitroprusside for ≥ 12 hours.

Design

The intent of this trial is to define the durability of the blood pressure effect of Nitroprusside in a pediatric population, to characterize the potential for rebound hypertension following Nitroprusside withdrawal, and to assess the potential development of tolerance. The doses to be used in this trial will be derived from the first study.

Enrolled patients will require relatively long-term controlled hypotension (≥ 12 hours). These patients could include patients who require ECMO (post surgical) or are post-operative following organ transplants (*e.g.*, kidney or liver). For one or more periods of one-half hour during the > 12 hour of infusion, the infusate should be replaced, in a blinded fashion, either with placebo or nitroprusside at the same concentration and changes in BP measured over the following 30 minutes. If the blood pressure rises above some pre-specified level or if the patient completes the 30-minute period, the patient should be returned to the previous stable infusion rate of Nitroprusside.

Frequent measurement of vital signs is also necessary for the first 30 minutes following initiation of Nitroprusside, and for 15 minutes following any dose-escalation of

Nitroprusside. Once a stable dose of Nitroprusside has been identified (3 successive systolic blood pressure readings within 5 mm Hg) vital signs can be obtained less frequently at the discretion of the investigators (*e.g.*, every 15 minutes).

Safety

The following items are required in addition to the standard collection of safety events.

- Significant hypotension will be defined by the investigators and its occurrence monitored during the trial.
- Adverse events occurring from the initial time of Nitroprusside administration until hospital discharge will be systematically collected and reported. Any adverse events that occur during surgery, during the recovery room period as well as during the duration of hospital stay will be captured and submitted as part of the study report, as will any need for drug intervention (including altering the degree of anesthesia). The circumstances of any deaths, discontinuations and serious adverse events should be adequately documented and transmitted within the study report. Patient with ongoing adverse events at the time of hospital discharge should be followed until resolution of adverse event.
- Methemoglobin levels should be frequently monitored. Thiocyanate and cyanide levels should also be monitored during the Nitroprusside infusion.

Inclusion/Exclusion Criteria

Any pediatric patients who require use of intravenous therapy for the reduction of blood pressure for at least 12 hours are eligible for enrollment if otherwise appropriate. The prior use of other drugs to lower BP should neither exclude patients from consideration nor a requirement of entry.

Number of patients to be studied/duration of exposure

The trial will be sized to detect the loss of as little as 50 percent of the expected blood pressure lowering effect of the chosen dose of nitroprusside during the 30 minutes of Nitroprusside withdrawal to placebo (based on the results from the first trial) with a power of 80% and an overall alpha level of 0.05 when compared with the patients who continue on Nitroprusside.

Data Analysis

It is unclear if a micro-assay requiring < 0.2 cc of blood exists which can accurately measure Nitroprusside levels *ex vivo*. If such an assay is available it should be used in the performance of pharmacokinetic/pharmacodynamic analysis and in assessing the relationship between Nitroprusside concentrations *in vivo* and any observed toxicities. As the primary intent of the present study is to describe the use of Nitroprusside in pediatric population, understanding the relationship between infusion rate and BP is of primary importance.

The goals of this study are to describe the relationship between rate of Nitroprusside infusion and changes in BP during longer-term administration (≥ 12 hours) of Nitroprusside. The model will analyze potential interactions of relevant demographics (*e.g.*, baseline blood pressure, age, gender, race and body size) with the time-course of the onset of blood pressure lowering effects of Nitroprusside as well as the time-course of blood pressure increases following nitroprusside discontinuation. The occurrence of rebound hypertension, the development of tolerance to the blood pressure lowering effects of Nitroprusside and the effects of Nitroprusside on heart rate are also of particular interest in this trial.

Long-term safety

Patients in the trial(s) of clinical efficacy should be followed for safety outcomes (adverse events), growth (change in head circumference weight, and length or height), and development (milestones, school performance, or neurocognitive testing) assessed at baseline and at one year.

- Response to Written Request: As per the Best Pharmaceuticals for Children Act, section 409I, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of NIH.